Metabolomic Profiling of the Effects of Dapagliflozin in Heart Failure with Reduced Ejection Fraction: DEFINE-HF

Supplementary Material

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Supplementary Table 1. List of metabolite symbols and names

Metabolite Symbol	Trivial name(s)
C2	Acetyl carnitine
C3	Propionyl carnitine
C*i*4-DC/C4-DC	Methylmalonyl carnitine or Succinyl carnitine
C4/C*i*4	Butyryl carnitine or Isobutyryl carnitine
C4-OH	3-Hydroxy-butyryl carnitine, b-hydroxy butyryl carnitine
C5:1	Tiglyl carnitine
C5's	Isovaleryl carnitine, 3-methylbutyryl carnitine or 2-Methylbutyryl carnitine
C5-DC	Glutaryl carnitine
C5-OH/C3-DC	3-Hydroxy-isovaleryl carnitine or Malonyl carnitine
C6	Hexanoyl carnitine
C6-DC	Adipoyl carnitine
C7-DC	Pimeloyl carnitine, heptanedioyl carnitine
C8	Octanoyl carnitine
C8:1	Octenoyl carnitine
C8:1-DC	Octenedioyl carnitine
C8:1-OH/C6:1-DC	3-Hydroxy-*cis*-5-octenoyl carnitine or Hexenedioyl carnitine
C10:3	Decatrienoyl carnitine
C10:2	Decadienoyl carnitine
C10:1	Decenoyl carnitine
C10	Decanoyl carnitine
C10-OH/C8-DC	3-Hydroxy-decanoyl carnitine or Suberoyl carnitine
C12:1	Dodecenoyl carnitine
C12	Lauroyl carnitine
C12-OH/C10-DC	3-Hydroxy-dodecanoyl carnitine or Sebacoyl carnitine
C14:2	Tetradecadienoyl carnitine
C14:1	Tetradecenoyl carnitine
C14	Myristoyl carnitine
C14:1-OH	3-Hydroxy-tetradecenoyl carnitine
C14-OH/C12-DC	3-Hydroxy-tetradecanoyl carnitine or Dodecanedioyl carnitine
C16	Palmitoyl carnitine
C16-OH/C14-DC	3-Hydroxy-hexadecanoyl carnitine or Tetradecanedioyl carnitine

Metabolite Symbol	**Trivial name(s)**
C16:2	Hexadecadienoyl carnitine
C16:1	Palmitoleoyl carnitine
C16:1-OH/C14:1-DC	3-Hydroxy-palmitoleoyl carnitine or *cis*-5-Tetradecenedioyl carnitine
C18:2-OH	3-Hydroxy-linoleyl carnitine
C18:2	Linoleyl carnitine
C18:1	Oleyl carnitine
C18	Stearoyl carnitine
C18:1-OH	3-Hydroxy-octadecenoyl carnitine
C18-OH/C16-DC	3-Hydroxy-octadecanoyl carnitine or Hexadecanedioyl carnitine, thapsoyl carnitine
C18:1-DC	Octadecenedioyl carnitine
C20	Arachidoyl carnitine, eicosanoyl carnitine
C20-OH/C18-DC	3-Hydroxy-eicosanoyl carnitine or Octadecanedioyl carnitine
C22	Behenoyl carnitine, docosanoyl carnitine
C20:4	Arachidonoyl carnitine
Ala	Alanine
Arg	Arginine
Asx	Asparagine + Aspartate
Cit	Citrulline
Glx	Glutamine + Glutamate
Gly	Glycine
His	Histidine
Leu/Ile	Leucine + Isoleucine
Met	Methionine
Orn	Ornithine
Phe	Phenylalanine
Pro	Proline
Ser	Serine
Tyr	Tyrosine
Val	Valine
NEFA	Nonesterified fatty acids
KET	Ketones
BHB	ß-hydroxybutyrate

Supplementary Table 2. Percentages of sample undetectability by metabolite.

Metabolite	Percent of samples undetectable
C7-DC	5.1
C22	4.9
C20	4.5
C5-DC	2.6
C18:1-OH/C16:1-DC	1.7
C12-OH/C10-DC	1.5
C16-OH/C14-DC	1.3
C18:2-OH	1.3
C4-OH	0.6
C6	0.6
C20:4	0.6
C18-OH/C16-DC	0.4
C4-DC/Ci4-DC	0.2
C12	0.2
C14-OH/C12-DC	0.2

Supplementary Table 3. Metabolites in each factor ranked by factor loads.

Factor1	Factor2	Factor3	Factor4	Factor5	Factor6	Factor7	Factor8	Factor9	Factor10	Factor11	Factor12	Factor13
C10	Phe	C18:1	C18-OH/C16-DC	Ser	3-Hydroxybutyrate	C8:1	Arg	C20:4	Ala	C3	Glx	C4-DC/Ci4-DC
C8	Met	C18	C18:1-DC	Gly	Total ketones	C10:3	Cit	C22	Pro	C5	Orn	C6-DC/C8-OH
C12	Tyr	C16	C18:1-OH/C16:1-DC	Asx	C4-OH	C10:2	Gly	C20	His	C4/Ci4	Tyr	C5-DC
C16:2	Leu/Ile	C18:2	C20-OH/C18-DC	C5:1	Nonesterified fatty acids	C10:1	Orn	C18:2	C14-OH/C12-DC	C5:1	Cit	C5-OH/C3-DC
C14:1	Val	C20	C16-OH/C14-DC	Met	C2	C8:1-DC	His	C14:1-OH	Leu/Ile	Val	Pro	C8:1-OH/C6:1-DC
C14:2	His	C16:1	C14-OH/C12-DC	C14:1-OH	C10-OH/C8-DC	C12:1	C16-OH/C14-DC	C2	Val	Leu/Ile	Gly	C7-DC
C14	C5	C14	C18:2-OH	C12-OH/C10-DC	C6-DC/C8-OH	C8:1-OH/C6:1-DC	C22	Asx	C16-OH/C14-DC	C5-OH/C3-DC	His	C10-OH/C8-DC
C6	Orn	C20:4	C16:1-OH/C14:1-DC	C10-OH/C8-DC	C12-OH/C10-DC	C2	Asx	C10:1	C18:1-DC	C2	C3	C4/Ci4
C10:1	Ser	C6	C14:1-OH	C6-DC/C8-OH	C14-OH/C12-DC	C6-DC/C8-OH	C8:1-OH/C6:1-DC	C6	Met	Nonesterified fatty acids	C4-DC/Ci4-DC	C8:1-DC
C16:1	C22	C16:1-OH/C14:1-DC	C12-OH/C10-DC	Orn	C14:1	C4-DC/Ci4-DC	Ser	C10-OH/C8-DC	Asx	C4-DC/Ci4-DC	C5:1	C12-OH/C10-DC
C12:1	Ala	C16:2	C10-OH/C8-DC	C12:1	C18:1-OH/C16:1-DC	C14:2	Pro	C12:1	Glx	Ser	C6-DC/C8-OH	Val
C5-DC	Arg	C14:1	C12:1	Glx	C14:2	C10-OH/C8-DC	C5:1	Pro	C20:4	Orn	C14-OH/C12-DC	Cit
C7-DC	C18:1-DC	C14:1-OH	C8:1-DC	C16	C18:1	C18:2	C14-OH/C12-DC	C8:1-DC	C18:1-OH/C16:1-DC	C5-DC	C8:1-OH/C6:1-DC	C2

C12-OH/C10-DC	C3	C18:2-OH	C7-DC	C18:2	C14:1-OH	C14:1-OH	C18-OH/C16-DC	C10:2	Gly	C4-OH	C18:1-DC	C18:2-OH
C10-OH/C8-DC	C5-OH/C3-DC	C18:1-OH/C16:1-DC	C14:1	C10:2	Ala	C7-DC	Met	C12-OH/C10-DC	C4-OH	Tyr	C18:2	C14:1-OH
C8:1-DC	C16-OH/C14-DC	C2	C14:2	His	C18:2-OH	C12-OH/C10-DC	C4-OH	C10:3	C6-DC/C8-OH	Phe	C20:4	Leu/Ile
C14:1-OH	Asx	C14:2	C4-OH	C20:4	Leu/Ile	C4-OH	C4-DC/Ci4-DC	Val	3-Hydroxybutyrate	C18-OH/C16-DC	C20	C12
C16	C4-OH	C22	C6-DC/C8-OH	C18:1-OH/C16:1-DC	C16:2	C18:1-DC	C16	His	Total ketones	C8:1	C10-OH/C8-DC	C10:3
C16:1-OH/C14:1-DC	C6-DC/C8-OH	Arg	C2	Nonesterified fatty acids	C16:1-OH/C14:1-DC	C14:1	Leu/Ile	C18:1-DC	C20-OH/C18-DC	C20:4	C4/Ci4	C4-OH
C18:1	C12:1	C12:1	C10:1	C4-DC/Ci4-DC	C12:1	C18:2-OH	C20-OH/C18-DC	C14-OH/C12-DC	Arg	Glx	C5	C20-OH/C18-DC
C8:1-OH/C6:1-DC	Pro	Orn	C16	C16:1-OH/C14:1-DC	C16	C16:2	C6	C5:1	C20	C8:1-OH/C6:1-DC	C18-OH/C16-DC	Ser
C10:2	C20-OH/C18-DC	C5-OH/C3-DC	C18	C14-OH/C12-DC	Ser	Ser	C14	C18:1	C18:1	C16:1	C8:1	C12:1
C14-OH/C12-DC	C18:2-OH	Gly	C8:1-OH/C6:1-DC	Pro	C16:1	C3	C8:1	C14	C2	C6	C4-OH	C10:2
C2	C2	C10:3	Cit	C18	C3	C6	C20:4	C16:1	C14	C8:1-DC	C20-OH/C18-DC	C18:1-DC
Nonesterified fatty acids	Cit	C12	C18:1	C5-OH/C3-DC	C4-DC/Ci4-DC	C20-OH/C18-DC	Ala	C14:2	C14:2	Met	C22	C14
C18:1-DC	C4-DC/Ci4-DC	3-Hydroxybutyrate	C14	C22	Tyr	C5-OH/C3-DC	Val	C6-DC/C8-OH	C16	C22	Val	C14:1
C18:2	C5-DC	Total ketones	Ser	C8:1-DC	Val	Cit	C16:1	Nonesterified fatty acids	C14:1	Gly	Leu/Ile	Phe

C18:1-OH/C16:1-DC	C12-OH/C10-DC	C18-OH/C16-DC	C4-DC/Ci4-DC	C12	Asx	Arg	C10:1	C4-OH	C18:2	C18	C12-OH/C10-DC	C5
C18	C4/Ci4	C18:1-DC	C12	C14	C18:1-DC	Phe	C3	C20-OH/C18-DC	C5-OH/C3-DC	C16-OH/C14-DC	C5-DC	Pro
C4-DC/Ci4-DC	C8:1	C3	Total ketones	C16-OH/C14-DC	C14	C22	C7-DC	Met	C18	Cit	C5-OH/C3-DC	Orn
C6-DC/C8-OH	C7-DC	Nonesterified fatty acids	3-Hydroxybutyrate	C18-OH/C16-DC	Pro	C14-OH/C12-DC	C5	Leu/Ile	C12-OH/C10-DC	C16	C18:1-OH/C16:1-DC	C3
C20-OH/C18-DC	C8:1-DC	C10:1	Ala	Leu/Ile	C18:2	Orn	C10:3	C16:1-OH/C14:1-DC	C16:1-OH/C14:1-DC	Ala	C12	C16-OH/C14-DC
C20	C20	C4-OH	C16:2	C14:1	C12	C18:1	C18:2-OH	Gly	C10:3	C8	Ala	C18-OH/C16-DC
C4-OH	C5:1	C8:1	C16:1	C5-DC	C8:1	C16:1	C12-OH/C10-DC	Cit	Nonesterified fatty acids	C18:1-DC	C14	C14-OH/C12-DC
C18:2-OH	C18-OH/C16-DC	Val	C10:2	C6	C22	C16:1-OH/C14:1-DC	C4/Ci4	C14:1	C18:2-OH	C14:2	C18:1	C16:1-OH/C14:1-DC
His	C10-OH/C8-DC	Leu/Ile	Met	C18:1-DC	C5-DC	His	C6-DC/C8-OH	C8	C10:1	C14-OH/C12-DC	Arg	C22
3-Hydroxybutyrate	C14:1-OH	C10-OH/C8-DC	C3	C16:2	C5:1	Met	C16:1-OH/C14:1-DC	C16:2	C22	C14:1	C12:1	C5:1
C5	C8	C8:1-OH/C6:1-DC	C20:4	C20-OH/C18-DC	Glx	Gly	Glx	C4-DC/Ci4-DC	C12:1	C18:2-OH	C14:1	Nonesterified fatty acids
Total ketones	Glx	C14-OH/C12-DC	Nonesterified fatty acids	Phe	C16-OH/C14-DC	C16	C16:2	C10	C8:1-DC	C10-OH/C8-DC	Phe	Arg
C18-OH/C16-DC	C10:2	Ala	C5:1	Arg	C6	C12	C14:2	Tyr	Cit	C12-OH/C10-DC	C2	C16:1
C8:1	Gly	C4-DC/Ci4-DC	Arg	C8	C7-DC	Nonesterified fatty acids	C8:1-DC	C5-DC	C18-OH/C16-DC	C20-OH/C18-DC	C10:1	C18:1

C22	C10	C20-OH/C18-DC	C4/Ci4	C4/Ci4	C18-OH/C16-DC	C20	C10:2	C4/Ci4	C12	C18:1-OH/C16:1-DC	C7-DC	C8:1
Ser	C14	Phe	C10:3	C14:2	C8:1-OH/C6:1-DC	Pro	C14:1	C3	Ser	C16:2	C8:1-DC	C20:4
Val	C18:1-OH/C16:1-DC	Cit	Val	C4-OH	C8:1-DC	Tyr	C18:1-OH/C16:1-DC	Arg	C4/Ci4	C10:2	C10:2	C16
Asx	C10:3	Glx	C8:1	Ala	C10:1	C5	C5-DC	C8:1	C5-DC	C12:1	C14:2	C6
C10:3	C6	C4/Ci4	C5-DC	C2	Arg	3-Hydroxybutyrate	C2	C5-OH/C3-DC	C8:1	Asx	C6	C10
Orn	C16	C12-OH/C10-DC	C10	C10:1	Met	C16-OH/C14-DC	C10	Ala	C5:1	His	C10:3	C14:2
Phe	C16:1-OH/C14:1-DC	Asx	His	C16:1	C18	C14	C18:1-DC	C12	C5	C10	Met	Gly
C16-OH/C14-DC	C18:2	C10:2	Leu/Ile	3-Hydroxybutyrate	Orn	Total ketones	C18:1	C16	C7-DC	C10:1	C16:1-OH/C14:1-DC	Asx
Glx	C8:1-OH/C6:1-DC	C6-DC/C8-OH	Glx	C7-DC	C5	Ala	C18:2	C18:2-OH	C10-OH/C8-DC	C16:1-OH/C14:1-DC	Ser	C20
Pro	C20:4	C10	C18:2	C10	C10:3	Val	Tyr	C18	C6	C14:1-OH	C18:2-OH	Glx
C20:4	C12	C8:1-DC	C5-OH/C3-DC	C3	C20	C5-DC	C14:1-OH	C16-OH/C14-DC	C8:1-OH/C6:1-DC	C18:2	C8	Total ketones
Tyr	C10:1	C8	C8	C18:1	Cit	Leu/Ile	Nonesterified fatty acids	C7-DC	C10:2	C10:3	C16-OH/C14-DC	Met
C5-OH/C3-DC	C14:1	C16-OH/C14-DC	C22	C10:3	C20-OH/C18-DC	C8	3-Hydroxybutyrate	Glx	Tyr	C7-DC	C16:1	Ala
Arg	C18:1	C5:1	Tyr	Total ketones	C8	C5:1	C5-OH/C3-DC	Orn	Orn	Pro	C16:2	C18:1-OH/C16:1-DC
C4/Ci4	C16:2	Ser	Asx	C5	His	C20:4	C12	C5	C14:1-OH	C12	C16	C18:2

C5:1	C14:2	Tyr	Gly	Val	C5-OH/C3-DC	C18	C18	C8:1-OH/C6:1-DC	C16:1	C6-DC/C8-OH	C18	Tyr
Met	C18	Met	C5	Cit	Phe	C18:1-OH/C16:1-DC	C10-OH/C8-DC	C18:1-OH/C16:1-DC	C3	C14	C14:1-OH	C10:1
C3	Total ketones	His	Pro	C20	C10	C4/Ci4	Total ketones	Phe	C4-DC/Ci4-DC	3-Hydroxybutyrate	C10	C18
Leu/Ile	C14-OH/C12-DC	Pro	C20	C18:2-OH	Gly	Glx	C12:1	3-Hydroxybutyrate	C16:2	C20	Total ketones	C16:2
Gly	C16:1	C7-DC	Orn	C8:1-OH/C6:1-DC	C20:4	Asx	Phe	C18-OH/C16-DC	C10	Total ketones	3-Hydroxybutyrate	His
Ala	3-Hydroxybutyrate	C5	Phe	C8:1	C10:2	C18-OH/C16-DC	C20	Ser	C8	C18:1	Nonesterified fatty acids	C8
Cit	Nonesterified fatty acids	C5-DC	C6	Tyr	C4/Ci4	C10	C8	Total ketones	Phe	Arg	Asx	3-Hydroxybutyrate

Highlighted in color if an absolute value of factor loads >0.4. Green indicates a positive factor load, while red indicates a negative factor load.

Supplementary Table 4. Baseline characteristics of patients in the full trial population and metabolomics subset

Characteristic	Full trial population N = 263	Metabolomics subset N = 234
Demographics		
Age, y	61 (12)	62 (11)
Female	70 (26.6%)	58 (24.8%)
Race		
White	144 (54.8%)	131 (56.0%)
African American	99 (37.6%)	88 (37.6%)
Other	20 (7.6%)	15 (6.4%)
Medical history		
Duration of heart failure, y	7.13 (6.30)	7.12 (6.26)
Previous hospitalization for heart failure	209 (79.5%)	187 (79.9%)
Time since last hospitalization for heart failure, y	1.61 (2.73)	1.69 (2.85)
Missing	54	47
Ejection fraction, %	27 (8)	27 (8)
Ischemic heart disease	139 (52.9%)	123 (52.6%)
Type 2 diabetes mellitus	166 (63.1%)	149 (63.7%)
Atrial Fibrillation	106 (40.3%)	99 (42.3%)
ICD	63 (62.0%)	143 (61.1%)
CRT		
No	95 (58.3%)	85 (59.4%)
Yes	68 (42.7%)	58 (40.6%)
Missing	100	91
Baseline HF/CV medications		
ACEI/ARB	141 (53.6%)	129 (55.1%)
ARNI	85 (32.3%)	72 (30.8%)
ß-blocker	254 (96.6%)	227 (97.0%)
Hydralazine	45 (17.1%)	45 (19.2%)
Long-acting nitrates	86 (32.7%)	80 (34.2%)
MRA	160 (60.8%)	143 (61.1%)
Loop diuretics	225 (85.6%)	199 (85.0%)
Digoxin	217 (82.5%)	190 (81.2%)
Lipid-lowering agents	211 (80.2%)	191 (81.6%)
Anticoagulant agent	100 (38.0%)	91 (38.9%)
Physical exam		
Body mass index (median Q1, Q3)	30.6 (27.5, 36.3)	31.0 (27.5, 36.2)

Characteristic	Full trial population N = 263	Metabolomics subset N = 234
Missing	5	4
Heart rate	72 (12)	72 (12)
Missing	14	12
Systolic blood pressure	124 (20)	124 (20)
Missing	1	1
Baseline laboratory studies		
NT-proBNP, pg/mL (median Q1, Q3)	1,136 (615, 2,266)	1,132 (616, 2,193)
Missing	3	2
BNP, pg/mL (median Q1, Q3)	269 (143, 567)	267 (145, 556)
Missing	3	2
eGFR, mL/min/1.73m^2	69 (22)	68 (21)
Urine albumin/creatinine ratio, mg/g (median Q1, Q3)	22 (7, 95)	24 (7, 97)
Missing	25	24
Hemoglobin A1c, %	7.2 (1.9)	7.1 (1.8)
Missing	1	1
Hemoglobin, g/dL	13.4 (1.8)	13.4 (1.8)
Missing	6	4
Functional measures		
NYHA Class		
Class II	173 (65.8%)	159 (67.95%)
Class III	90 (34.2%)	75 (32.05%)
KCCQ-OS	67 (21)	67 (22)
KCCQ-CS	70 (22)	70 (22)
6-minute walk distance, meters (median Q1, Q3)	305 (229, 369)	305 (227, 369)
Missing	2	1

Data presented as mean (standard deviation), median (interquartile range), or n (%).
ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; CSS, Clinical Summary Score; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; OSS, Overall Summary Score; NT-proBNP, N-terminal pro-B-type natriuretic peptide

Supplementary Table 5. Baseline characteristics of patients in the metabolomics subset and patients excluded from the subset

Characteristic	Metabolomics subset N = 234	Exclusion subset N = 29	p-value
Demographics			
Age, y	62 (11)	55 (14)	0.016
Male	176 (75.2%)	17 (58.6%)	0.057
Race			0.11
White	131 (56.0%)	13 (44.8%)	
African American	88 (37.6%)	11 (37.9%)	
Other	15 (6.4%)	5 (17.2%)	
Medical history			
Duration of heart failure, y	7.12 (6.26)	7.24 (6.69)	0.92
Previous hospitalization for heart failure	187 (79.9%)	22 (75.9%)	0.61
Time since last hospitalization for heart failure, y	1.69 (2.85)	0.91 (1.18)	0.021
Missing	47	7	
Ejection fraction, %	27 (8)	26 (8)	0.56
Ischemic heart disease	123 (52.6%)	16 (55.2%)	0.79
Type 2 diabetes mellitus	149 (63.9%)	17 (58.6%)	0.59
Atrial Fibrillation	99 (42.3%)	7 (24.1%)	0.060
ICD	143 (61.1%)	20 (69.0%)	0.41
CRT			0.42
No	85 (59.4%)	10 (50.0%)	
Yes	58 (40.6%)	10 (50.0%)	
Missing	91	9	
Baseline HF/CV medications			
ACEI/ARB	129 (55.1%)	12 (41.3%)	0.16
Angiotensin receptor neprilysin inhibitor	72 (30.8%)	13 (44.8%)	0.13
ß-blocker	227 (97.0%)	27 (93.1%)	0.26
Hydralazine	45 (19.2%)	0 (0.0%)	0.007
Long-acting nitrates	80 (34.2%)	6 (20.7%)	0.14
MRA	143 (61.1%)	17 (58.6%)	0.80
Loop diuretics	199 (85.0%)	26 (89.7%)	0.78
Digoxin	44 (18.8%)	2 (6.9%)	0.11
Lipid-lowering agents	191 (81.6%)	20 (69.0%)	0.11
Anticoagulant agent	91 (38.9%)	9 (31.0%)	0.41

Characteristic	Metabolomics subset N = 234	Exclusion subset N = 29	p-value
Glucose lowering medications among patients with type 2 diabetes mellitus			
Insulin	76 (51.0%)	11 (64.7%)	0.28
GLP-1RA	4 (2.7%)	1 (5.89%)	0.42
DPP4-inhibitor	19 (12.7%)	2 (11.8%)	>0.99
Sulfonylurea	32 (21.5%)	3 (17.7%)	>0.99
Metformin	56 (37.6%)	6 (35.3%)	0.85
Physical exam			
Body mass index (median Q1, Q3)	31.0 (27.5, 36.2)	30.0 (26.7, 36.7)	0.74
Missing	4	1	
Heart rate[3]	72 (12)	72 (13)	0.85
Missing	12	2	
Systolic blood pressure[3]	124 (20)	119 (22)	0.19
Missing	1	0	
Baseline laboratory studies			
NT-proBNP, pg/mL (median Q1, Q3)	1,132 (616, 2,193)	1,406 (553, 2,372)	0.96
Missing	2	1	
BNP, pg/mL (median Q1, Q3)	267 (145, 556)	340 (122, 629)	0.74
Missing	2	1	
eGFR, mL/min/1.73m^2	68 (21)	76 (27)	0.17
Urine albumin/creatinine ratio, mg/g (median Q1, Q3)	24 (7, 97)	19 (7, 52)	0.42
Missing	24	1	
Hemoglobin A1c, %	7.1 (1.8)	7.9 (2.8)	0.12
Missing	1	0	
Hemoglobin, g/dL	13.4 (1.8)	13.2 (1.9)	0.59
Missing	4	2	
Functional measures			
NYHA Class			0.035
Class II	159 (68.0%)	14 (48.3%)	
Class III	75 (32.1%)	15 (51.7%)	
KCCQ-OS	67 (22)	70 (19)	0.39
KCCQ-CS	70 (22)	73 (20)	0.38
6-minute walk distance, meters (median Q1, Q3)	305 (227, 369)	314 (254, 354)	0.82
Missing	1	1	

Characteristic	Metabolomics subset N = 234	Exclusion subset N = 29	p-value

Data presented as mean (standard deviation), median (interquartile range), or n (%).
ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; CSS, Clinical Summary Score; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; OSS, Overall Summary Score; NT-proBNP, N-terminal pro-B-type natriuretic peptide

Supplementary Table 6. Baseline individual metabolite levels by treatment groups

Class	Metabolites	Dapagliflozin	Placebo	p-value
Amino acid (μM)	Gly	326.41 (72.92)	308.66 (55.56)	0.04
Amino acid (μM)	Ala	444.78 (105.87)	401.90 (94.01)	0.00
Amino acid (μM)	Ser	96.41 (19.10)	97.12 (21.32)	0.79
Amino acid (μM)	Pro	223.33 (71.34)	204.60 (61.18)	0.03
Amino acid (μM)	Val	247.42 (59.11)	238.26 (46.62)	0.19
Amino acid (μM)	Leu/Ile	178.29 (42.40)	170.75 (31.94)	0.12
Amino acid (μM)	Met	26.95 (5.96)	26.54 (5.25)	0.58
Amino acid (μM)	His	75.82 (9.67)	75.25 (11.60)	0.68
Amino acid (μM)	Phe	67.11 (10.00)	67.37 (11.43)	0.85
Amino acid (μM)	Tyr	71.94 (18.95)	69.40 (14.97)	0.25
Amino acid (μM)	Asx	63.12 (23.68)	58.09 (13.40)	0.05
Amino acid (μM)	Glx	123.99 (48.30)	122.30 (46.32)	0.79
Amino acid (μM)	Orn	89.29 (31.64)	86.58 (28.54)	0.49
Amino acid (μM)	Cit	42.05 (14.70)	41.00 (13.43)	0.57
Amino acid (μM)	Arg	72.63 (21.48)	71.95 (17.98)	0.79
Acylcarnitine (μM)	C2	10.29 (4.08)	10.03 (3.46)	0.60
Acylcarnitine (μM)	C3	0.4750 (0.1803)	0.4429 (0.1631)	0.15
Acylcarnitine (μM)	C4/Ci4	0.3017 (0.1674)	0.2722 (0.1481)	0.15
Acylcarnitine (μM)	C5:1	0.0641 (0.0178)	0.0628 (0.0157)	0.56
Acylcarnitine (μM)	C5	0.1655 (0.0748)	0.1656 (0.0699)	0.99
Acylcarnitine (μM)	C4-OH	0.0702 (0.0605)	0.0660 (0.0434)	0.55
Acylcarnitine (μM)	C6	0.0946 (0.0605)	0.0912 (0.0639)	0.68
Acylcarnitine (μM)	C5-OH/C3-DC	0.0477 (0.0165)	0.0484 (0.0223)	0.77
Acylcarnitine (μM)	C4-DC/Ci4-DC	0.0540 (0.0203)	0.0515 (0.0176)	0.32
Acylcarnitine (μM)	C8:1	0.4268 (0.2073)	0.3929 (0.1757)	0.18
Acylcarnitine (μM)	C8	0.2027 (0.1356)	0.1997 (0.2050)	0.89
Acylcarnitine (μM)	C5-DC	0.0670 (0.0358)	0.0648 (0.0320)	0.62
Acylcarnitine (μM)	C8:1-OH/C6:1-DC	0.0425 (0.0175)	0.0389 (0.0176)	0.12
Acylcarnitine (μM)	C6-DC/C8-OH	0.1133 (0.0586)	0.1102 (0.0581)	0.68
Acylcarnitine (μM)	C10:3	0.1225 (0.0547)	0.1207 (0.0574)	0.81
Acylcarnitine (μM)	C10:2	0.0346 (0.0137)	0.0345 (0.0146)	0.93
Acylcarnitine (μM)	C10:1	0.2195 (0.0964)	0.2097 (0.1038)	0.46
Acylcarnitine (μM)	C10	0.3072 (0.2216)	0.3031 (0.3043)	0.91
Acylcarnitine (μM)	C7-DC	0.0223 (0.0094)	0.0223 (0.0101)	0.96
Acylcarnitine (μM)	C8:1-DC	0.0479 (0.0187)	0.0455 (0.0217)	0.38
Acylcarnitine (μM)	C10-OH/C8-DC	0.0747 (0.0296)	0.0745 (0.0341)	0.97
Acylcarnitine (μM)	C12:1	0.1475 (0.0610)	0.1424 (0.0708)	0.56
Acylcarnitine (μM)	C12	0.1088 (0.0639)	0.1061 (0.0756)	0.77
Acylcarnitine (μM)	C12-OH/C10-DC	0.0162 (0.0068)	0.0155 (0.0074)	0.44
Acylcarnitine (μM)	C14:2	0.0668 (0.0329)	0.0675 (0.0419)	0.89
Acylcarnitine (μM)	C14:1	0.1045 (0.0557)	0.1055 (0.0650)	0.90
Acylcarnitine (μM)	C14	0.0384 (0.0193)	0.0376 (0.0193)	0.77
Acylcarnitine (μM)	C14:1-OH	0.0193 (0.0078)	0.0184 (0.0079)	0.37
Acylcarnitine (μM)	C14-OH/C12-DC	0.0110 (0.0055)	0.0105 (0.0052)	0.54
Acylcarnitine (μM)	C16:2	0.0127 (0.0089)	0.0126 (0.0098)	0.93
Acylcarnitine (μM)	C16:1	0.0321 (0.0236)	0.0305 (0.0175)	0.55
Acylcarnitine (μM)	C16	0.1052 (0.0353)	0.1037 (0.0306)	0.72

Acylcarnitine (μM)	C16:1-OH/C14:1-DC	0.0097 (0.0036)	0.0097 (0.0035)	0.96
Acylcarnitine (μM)	C16-OH/C14-DC	0.0070 (0.0041)	0.0060 (0.0027)	0.03
Acylcarnitine (μM)	C18:2	0.0890 (0.0373)	0.0917 (0.0344)	0.56
Acylcarnitine (μM)	C18:1	0.1451 (0.0606)	0.1479 (0.0588)	0.71
Acylcarnitine (μM)	C18	0.0489 (0.0172)	0.0484 (0.0147)	0.82
Acylcarnitine (μM)	C18:2-OH	0.0058 (0.0021)	0.0060 (0.0021)	0.62
Acylcarnitine (μM)	C18:1-OH/C16:1-DC	0.0071 (0.0038)	0.0063 (0.0034)	0.11
Acylcarnitine (μM)	C18-OH/C16-DC	0.0097 (0.0047)	0.0093 (0.0046)	0.51
Acylcarnitine (μM)	C20:4	0.0090 (0.0038)	0.0093 (0.0047)	0.54
Acylcarnitine (μM)	C20	0.0057 (0.0064)	0.0048 (0.0025)	0.19
Acylcarnitine (μM)	C18:1-DC	0.0139 (0.0065)	0.0149 (0.0088)	0.31
Acylcarnitine (μM)	C20-OH/C18-DC	0.0138 (0.0059)	0.0148 (0.0071)	0.26
Acylcarnitine (μM)	C22	0.0044 (0.0023)	0.0047 (0.0025)	0.38
Conventional metabolite (μmol/L)	3-Hydroxybutyrate	81.12 (91.54)	97.75 (95.94)	0.18
Conventional metabolite (μmol/L)	Total ketones	105.17 (110.12)	124.39 (109.87)	0.18
Conventional metabolite (mmol/L)	NEFA	0.4999 (0.2453)	0.5290 (0.2727)	0.39

Concentrations reported as mean (standard deviation).

Supplementary Table 7. Interaction analysis of treatment and background use of medical therapies on principal components analysis defined metabolite clusters

Factors	Annotations for factors	Treatment*MRA		Treatment*ARNI	
		Nominal P value	FDR corrected P value	Nominal P value	FDR corrected P value
Factor 1	Medium-chain acylcarnitines	0.81	0.82	0.62	0.82
Factor 2	Branched-chain and aromatic amino acids	0.70	0.82	0.95	0.95
Factor 3	Long-chain acylcarnitines	0.09	0.51	0.22	0.58
Factor 4	Long-chain dicarboxyl acylcarnitines	0.79	0.82	0.88	0.95
Factor 5	Miscellaneous amino acids	0.49	0.82	0.95	0.95
Factor 6	Ketone-related metabolites and short-chain acylcarnitines	0.12	0.51	0.20	0.58
Factor 7	Medium-chain acylcarnitines	0.82	0.82	0.31	0.67
Factor 8	Miscellaneous amino acids	0.20	0.66	0.01	0.18
Factor 9	Long-chain acylcarnitines	0.44	0.82	0.63	0.82
Factor 10	Miscellaneous amino acids	0.07	0.51	0.21	0.58
Factor 11	Branched-chain amino acids and short-chain acylcarnitines	0.64	0.82	0.21	0.58
Factor 12	Miscellaneous amino acids	0.51	0.82	0.58	0.82
Factor 13	Short-chain dicarboxyl acylcarnitines	0.37	0.82	0.44	0.82

Model adjusted for randomized treatment group, MRA or ARNI, baseline factor level, age, race/ethnicity, sex, eGFR, and type 2 diabetes mellitus.
FDR, false discovery rate; MRA, mineralocorticoid antagonist; ARNI, angiotensin-receptor/neprilysin inhibitor.

Supplementary Table 8. Longitudinal differences in metabolites by treatment group

Metabolites	PCA factors	Dapagliflozin, N = 121				Placebo, N = 113			
		Mean of the Differences	95% Confidence Interval		p-value	Mean of the Differences	95% Confidence Interval		p-value
			Lower level	Upper level			Lower level	Upper level	
C2	factor 6	1.0498	0.2997	1.7998	0.001	0.2227	-0.4667	0.9122	0.52
C4-OH	factor 6	0.0147	0.0051	0.0242	0.003	-0.0004	-0.0093	0.0085	0.93
3-Hydroxybutyrate	factor 6	29.3826	8.0970	50.6683	0.007	-17.0000	-35.4934	1.4934	0.07
Total ketones	factor 6	32.2620	6.7946	57.7294	0.02	-18.5637	-40.9366	3.8092	0.10
Nonesterified fatty acids	factor 6	0.0215	-0.0316	0.0746	0.42	-0.0396	-0.0961	0.0170	0.17
C8:1	factor 7	0.0432	0.0063	0.0801	0.02	0.0156	-0.0152	0.0464	0.32
C10:3	factor 7	0.0121	0.0027	0.0214	0.01	0.0003	-0.0082	0.0088	0.95
C10:2	factor 7	0.0051	0.0019	0.0083	0.002	-0.0002	-0.0027	0.0023	0.88
C10:1	factor 7	0.0120	-0.0066	0.0305	0.20	0.0036	-0.0158	0.0230	0.72
C8:1-DC	factor 7	0.0065	0.0026	0.0104	0.001	0.0001	-0.0032	0.0034	0.95
C12:1	factor 7	0.0076	-0.0058	0.0211	0.26	-0.0038	-0.0172	0.0096	0.57

Paired T-test used for statistical comparisons. Differences defined by follow-up visit minus baseline visit.
PCA, principal components analysis.

Supplementary Table 9. Placebo-adjusted changes in metabolites from baseline to follow-up

Metabolites	PCA factors	Placebo-adjusted mean of the differences	95% Confidence Interval		p-value
			Lower level	Upper level	
C2	factor 6	0.8270	-0.1864	1.8405	0.11
C4-OH	factor 6	0.0150	0.0020	0.0281	0.02
3-Hydroxybutyrate	factor 6	46.3826	18.3305	74.4348	0.001
Total ketones	factor 6	50.8257	17.1017	84.5497	0.003
Nonesterified fatty acids	factor 6	0.0610	-0.0161	0.1382	0.12
C8:1	factor 7	0.0276	-0.0202	0.0754	0.26
C10:3	factor 7	0.0118	-0.0008	0.0244	0.07
C10:2	factor 7	0.0053	0.0013	0.0093	0.01
C10:1	factor 7	0.0084	-0.0183	0.0351	0.54
C8:1-DC	factor 7	0.0064	0.0013	0.0115	0.01
C12:1	factor 7	0.0114	-0.0074	0.0303	0.23

Two samples T-test used for statistical comparisons. Differences defined by follow-up visit minus baseline visit.
PCA, principal components analysis.

Supplementary Table 10. Covariate predictors of change in beta-hydroxybutyrate levels in all study participants.

Characteristic	Estimates	95% confidence interval		p-value	LASSO p-value
		lower	upper		
Treatment arm	40.582	10.195	70.969	0.01	0.003
Baseline beta-hydroxybutyrate	-0.513	-0.675	-0.352	< 0.001	<0.001
Demographics					
Age, y	0.271	-1.729	2.271	0.80	-
Male	-61.237	-99.53	-22.943	0.002	-
Race					
African American	ref	ref	ref		
White	-4.699	-44.837	35.438	0.74	-
Other	-11.704	-80.567	57.159	0.82	-
Medical history					
Previous hospitalization for heart failure	6.112	-34.558	46.782	0.77	-
Ejection fraction, %	-0.804	-3.013	1.404	0.48	-
Ischemic heart disease	44.27	9.934	78.606	0.01	-
Type 2 diabetes mellitus	-5.521	-43.117	32.075	0.77	-
Atrial Fibrillation	36.548	3.812	69.284	0.03	-
Baseline HF/CV medications					
ACEI/ARB	-21.796	-64.117	20.524	0.31	-
Angiotensin receptor neprilysin inhibitor	-13.715	-60.383	32.953	0.57	-
ß-blocker	39.873	-48.173	127.918	0.38	-
Hydralazine	47.165	-1.451	95.78	0.06	-
Long-acting nitrates	-16.787	-53.277	19.702	0.37	-

Characteristic	Estimates	95% confidence interval		p-value	LASSO p-value
		lower	upper		
MRA	18.216	-14.344	50.777	0.27	-
Loop diuretics	-30.918	-76.171	14.334	0.18	-
Digoxin	-37.341	-79.243	4.562	0.08	-
Lipid-lowering agents	-56.691	-101.068	-12.314	0.01	0.009
Physical exam					
Body mass index	-0.434	-3.195	2.327	0.76	-
Heart rate	0.066	-1.313	1.446	0.93	-
Systolic blood pressure	-0.619	-1.446	0.208	0.14	-
Baseline laboratory studies					
NT-proBNP, pg/mL	-0.00041	-0.00743	0.00661	0.91	-
eGFR, mL/min/1.73m^2	1.109	0.254	1.965	0.01	-
Urine albumin/creatinine ratio, mg/g	0.031	0.007	0.056	0.01	-
Hemoglobin A1c, %	-7.022	-17.13	3.086	0.18	-
Functional measures					
NYHA Class					
Class II	ref	ref			
Class III	-20.529	-55.516	14.459	0.25	-
KCCQ-OSS	-0.619	-1.456	0.217	0.15	-
6-minute walk distance, meters	0.001	-0.179	0.182	0.99	-

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; LASSO, Least Absolute Shrinkage and Selection Operator; KCCQ, Kansas City Cardiomyopathy Questionnaire; OSS, Overall Summary Score; NT-proBNP, N-terminal pro-B-type natriuretic peptide

Supplementary Table 11. Association of baseline PCA metabolite factors with changes in quality of life and natriuretic peptides.

Baseline factor	Factor description	log NT-proBNP		KCCQ-OSS		KCCQ-CSS	
		Nominal P value	FDR corrected P value	Nominal P value	FDR corrected P value	Nominal P value	FDR corrected P value
Factor 1	Medium-chain acylcarnitines	0.59	0.99	0.10	0.36	0.38	0.81
Factor 2	Branched-chain and aromatic amino acids	0.26	0.85	0.04	0.36	0.06	0.73
Factor 3	Long-chain acylcarnitines	0.93	0.99	0.31	0.76	0.47	0.81
Factor 4	Long-chain dicarboxyl acylcarnitines	0.47	0.99	0.11	0.36	0.19	0.81
Factor 5	Miscellaneous amino acids	0.54	0.99	0.11	0.36	0.17	0.81
Factor 6	Ketone-related metabolites and short-chain acylcarnitines	0.09	0.57	0.59	0.76	0.44	0.81
Factor 7	Medium-chain acylcarnitines	0.90	0.99	0.45	0.76	0.43	0.81
Factor 8	Miscellaneous amino acids	0.65	0.99	0.65	0.76	0.75	0.84
Factor 9	Long-chain acylcarnitines	0.99	0.99	0.99	0.99	0.91	0.91
Factor 10	Miscellaneous amino acids	0.24	0.85	0.38	0.76	0.62	0.81
Factor 11	Branched-chain amino acids and short-chain acylcarnitines	0.69	0.99	0.55	0.76	0.77	0.84
Factor 12	Miscellaneous amino acids	0.91	0.99	0.88	0.95	0.57	0.81
Factor 13	Short-chain dicarboxyl acylcarnitines	0.08	0.57	0.51	0.76	0.62	0.81

Model adjusted for baseline value of the respective outcome, age, race/ethnicity, sex, eGFR, and type 2 diabetes mellitus.
CSS, clinical summary score; eGFR, estimated glomerular filtration rate; FDR, false discovery rate; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro B-type natriuretic peptide; OSS, overall summary score.

Supplementary Table 12. Association between changes in individual metabolites from significant PCA factors and changes in log NT-proBNP

Metabolites	PCA factors	per 1 μm increase in the metabolites			per 1 SD increase in the metabolites			P value
		Estimate	95% Confidence Interval		Estimate	95% Confidence Interval		
			Lower Level	Upper Level		Lower Level	Upper Level	
C6	Factor 3	0.7567	-0.4082	1.9215	0.0528	-0.0285	0.1342	0.20
C14	Factor 3	8.8555	4.1008	13.6101	0.1509	0.0699	0.2319	<0.001
C16:2	Factor 3	13.7736	5.2252	22.3219	0.1349	0.0512	0.2187	0.002
C16:1	Factor 3	8.5320	3.8868	13.1771	0.1532	0.0698	0.2365	<0.001
C16	Factor 3	5.5552	2.7980	8.3124	0.1657	0.0835	0.2480	<0.001
C16:1-OH/C14:1-DC	Factor 3 Factor 4	30.1686	9.8210	50.5162	0.1313	0.0427	0.2198	0.004
C18:2	Factor 4	3.1145	0.5086	5.7204	0.1009	0.0165	0.1854	0.02
C18:1	Factor 4	3.2750	1.7176	4.8324	0.1772	0.0929	0.2614	<0.001
C18	Factor 4	8.5264	2.7793	14.2734	0.1189	0.0388	0.1991	0.004
C20:4	Factor 4	11.1365	-13.1164	35.3893	0.0424	-0.0499	0.1346	0.37
C20	Factor 4	24.3769	-6.3662	55.1200	0.0650	-0.0170	0.1469	0.12
C10-OH/C8-DC	Factor 4	5.2665	2.7659	7.7672	0.1761	0.0925	0.2596	<0.001
C12:1	Factor 4	2.4091	1.2471	3.5711	0.1769	0.0916	0.2623	<0.001
C12-OH/C10-DC	Factor 4	27.2625	16.0086	38.5165	0.2028	0.1191	0.2865	<0.001
C14:1-OH	Factor 4	24.4947	14.0029	34.9865	0.2078	0.1188	0.2968	<0.001
C14-OH/C12-DC	Factor 4	32.4209	14.1851	50.6568	0.1671	0.0731	0.2611	<0.001
C16-OH/C14-DC	Factor 4	49.0450	22.8524	75.2375	0.1788	0.0833	0.2743	<0.001
C18:2-OH	Factor 4	47.0665	11.9816	82.1514	0.1307	0.0333	0.2281	0.009
C18:1-OH/C16:1-DC	Factor 4	71.3590	44.3613	98.3566	0.2658	0.1653	0.3664	<0.001
C18-OH/C16-DC	Factor 4	27.9584	8.0796	47.8371	0.1444	0.0417	0.2470	0.006
C18:1-DC	Factor 4	21.8630	10.9756	32.7504	0.1806	0.0907	0.2706	<0.001
C20-OH/C18-DC	Factor 4	18.1866	3.8063	32.5669	0.1127	0.0236	0.2018	0.01
Ala	Factor 10	-0.0008	-0.0017	0.0001	-0.0745	-0.1575	0.0076	0.08

Pro	Factor 10	-0.0019	-0.0033	-0.0005	-0.1104	-0.1926	-0.0276	0.001
His	Factor 10	-0.0091	-0.0170	-0.0011	-0.0939	-0.1760	-0.0117	0.03

Model adjusted for baseline metabolites level, baseline value of the respective outcome, age, race/ethnicity, sex, eGFR, and type 2 diabetes mellitus.

eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro B-type natriuretic peptide; SD, standard deviation.

Supplementary Table 13. Association between changes in individual metabolites from significant PCA factors and changes in KCCQ-OSS

Metabolites	PCA factors	per 1 μm increase in the metabolites			per 1 SD increase in the metabolites			P value
		Estimate	95% Confidence Interval		Estimate	95% Confidence Interval		
			Lower Level	Upper Level		Lower Level	Upper Level	
Val	Factor 2	-0.0254	-0.0703	0.0195	-1.1686	-3.2355	0.8984	0.27
Leu/Ile	Factor 2	-0.0472	-0.0960	0.0017	-1.9565	-3.9830	0.0701	0.06
Met	Factor 2	-0.2857	-0.5825	0.0111	-1.8932	-3.8598	0.0734	0.06
His	Factor 2	0.0254	-0.1625	0.2133	0.2634	-1.6857	2.2125	0.79
Phe	Factor 2	-0.2717	-0.4183	-0.1252	-3.4388	-5.2933	-1.5844	<0.001
Tyr	Factor 2	-0.2167	-0.3528	-0.0806	-2.9509	-4.8041	-1.0975	0.002
C6	Factor 2	-28.0918	-55.3097	-0.8739	-1.9613	-3.8616	-0.0610	0.04
C14	Factor 3	-224.7993	-335.2717	-114.3270	-3.8311	-5.7137	-1.9484	<0.001
C16:2	Factor 3	-356.5196	-555.0674	-157.9718	-3.4925	-5.4376	-1.5475	<0.001
C16:1	Factor 3	-208.8487	-317.2145	-100.4829	-3.7492	-5.6945	-1.8038	<0.001
C16	Factor 3	-151.7660	-215.7578	-87.7741	-4.5280	-6.4372	-2.6188	<0.001
C16:1-OH/C14:1-DC	Factors 3 and 4	-1038.4460	-1505.0844	-571.8076	-4.5182	-6.5485	-2.4879	<0.001
C18:2	Factor 3	-121.8782	-181.6297	-62.1268	-3.9501	-5.8867	-2.0136	<0.001
C18:1	Factor 3	-84.9478	-121.2790	-48.6166	-4.5959	-6.5616	-2.6303	<0.001
C18	Factor 3	-321.2520	-451.9517	-190.5523	-4.4803	-6.3031	-2.6575	<0.001
C20:4	Factor 3	-907.6343	-1464.9672	-350.3014	-3.4526	-5.5726	-1.3325	0.002
C20	Factor 3	10.7846	-710.3796	731.9488	0.0287	-1.8936	1.9511	0.98
C10-OH/C8-DC	Factor 4	-98.4560	-158.1035	-38.8086	-3.2912	-5.2851	-1.2973	0.001
C12:1	Factor 4	-37.8611	-65.7265	-9.9957	-2.7806	-4.8271	-0.7341	0.008
C12-OH/C10-DC	Factor 4	-638.2197	-902.6208	-373.8186	-4.7474	-6.7142	-2.7807	<0.001
C14:1-OH	Factor 4	-502.8506	-750.0533	-255.6478	-4.2654	-6.3623	-2.1685	<0.001
C14-OH/C12-DC	Factor 4	-597.4505	-1026.6952	-168.2058	-3.0790	-5.2912	-0.8669	0.007
C16-OH/C14-DC	Factor 4	-1003.7674	-1625.0527	-382.4822	-3.6601	-5.9256	-1.3947	0.002
C18:2-OH	Factor 4	-799.8900	-1630.7208	30.9407	-2.2207	-4.5274	0.0859	0.06
C18:1-OH/C16:1-DC	Factor 4	-1105.6420	-1745.5732	-465.7108	-4.1187	-6.5026	-1.7349	<0.001

C18-OH/C16-DC	Factor 4	-670.3198	-1134.2019	-206.4378	-3.4611	-5.8562	-1.0659	0.005
C18:1-DC	Factor 4	-473.6655	-728.5339	-218.7971	-3.9138	-6.0197	-1.8079	<0.001
C20-OH/C18-DC	Factor 4	-557.7662	-891.3908	-224.1417	-3.4554	-5.5222	-1.3886	0.001

Model adjusted for baseline metabolites level, baseline value of KCCQ-OSS, age, race/ethnicity, sex, eGFR, and type 2 diabetes mellitus.

eGFR, estimated glomerular filtration rate; KCCQ, Kansas City Cardiomyopathy Questionnaire; OSS, overall summary score; SD, standard deviation.

Supplementary Table 14. Association between changes in individual metabolites from significant PCA factors and changes in KCCQ-CSS

Metabolites	PCA factors	per 1 μm increase in the metabolites			per 1 SD increase in the metabolites			P value
		Estimate	95% Confidence Interval		Estimate	95% Confidence Interval		
			Lower Level	Upper Level		Lower Level	Upper Level	
Val	Factor 2	-0.0280	-0.0744	0.0184	-1.2887	-3.4224	0.8455	0.24
Leu/Ile	Factor 2	-0.0427	-0.0934	0.0080	-1.7710	-3.8760	0.3335	0.10
Met	Factor 2	-0.2636	-0.5732	0.0459	-1.7468	-3.7977	0.3041	0.10
His	Factor 2	-0.0085	-0.2035	0.1865	-0.0879	-2.1101	1.9343	0.93
Phe	Factor 2	-0.2533	-0.4049	-0.1017	-3.2054	-5.1241	-1.2866	0.001
Tyr	Factor 2	-0.1884	-0.3296	-0.0472	-2.5660	-4.4889	-0.6431	0.001
C6	Factor 3	-16.3054	-44.7043	12.0935	-1.1384	-3.1212	0.8443	0.26
C14	Factor 3	-173.1681	-290.0124	-56.3238	-2.9511	-4.9424	-0.9599	0.004
C16:2	Factor 3	-261.8969	-471.3399	-52.4538	-2.5656	-4.6173	-0.5138	0.02
C16:1	Factor 3	-152.9024	-267.5518	-38.2530	-2.7448	-4.8030	-0.6867	0.01
C16	Factor 3	-131.4214	-198.7189	-64.1239	-3.9210	-5.9288	-1.9131	<0.001
C16:1-OH/C14:1-DC	Factors 3 and 4	-910.6958	-1400.0609	-421.3306	-3.9624	-6.0915	-1.8332	<0.001
C18:2	Factor 3	-99.3278	-162.1287	-36.5270	-3.2193	-5.2547	-1.1839	0.002
C18:1	Factor 3	-67.5381	-105.8663	-29.2098	-3.6540	-5.7277	-1.5803	<0.001
C18	Factor 3	-293.1731	-430.1823	-156.1640	-4.0887	-5.9995	-2.1779	<0.001
C20:4	Factor 3	-915.2152	-1493.2457	-337.1846	-3.4814	-5.6802	-1.2826	0.002
C20	Factor 3	-242.2251	-989.8168	505.3667	-0.6457	-2.6385	1.3471	0.53
C10-OH/C8-DC	Factor 4	-56.2142	-118.5020	6.0735	-1.8791	-3.9613	0.2030	0.08
C12:1	Factor 4	-18.0521	-47.0276	10.9234	-1.3258	-3.4538	0.8022	0.22
C12-OH/C10-DC	Factor 4	-488.5785	-766.8659	-210.2911	-3.6343	-5.7044	-1.5643	<0.001
C14:1-OH	Factor 4	-319.4123	-579.5619	-59.2627	-2.7094	-4.9161	-0.5027	0.02
C14-OH/C12-DC	Factor 4	-482.9458	-927.0343	-38.8573	-2.4889	-4.7776	-0.2003	0.03
C16-OH/C14-DC	Factor 4	-745.4747	-1396.0123	-94.9370	-2.7183	-5.0904	-0.3462	0.03
C18:2-OH	Factor 4	-1014.4513	-1870.9372	-157.9654	-2.8164	-5.1943	-0.4386	0.02

C18:1-OH/C16:1-DC	Factor 4	-895.5127	-1567.1581	-223.8672	-3.3359	-5.8379	-0.8339	0.01
C18-OH/C16-DC	Factor 4	-743.2855	-1222.1830	-264.3880	-3.8378	-6.3105	-1.3651	0.003
C18:1-DC	Factor 4	-518.0911	-780.8140	-255.3682	-4.2809	-6.4517	-2.1101	<0.001
C20-OH/C18-DC	Factor 4	-507.6468	-855.1818	-160.1118	-3.1449	-5.2979	-0.9919	0.005

Model adjusted for baseline metabolites level, baseline value of KCCQ-CSS, age, race/ethnicity, sex, eGFR, and type 2 diabetes mellitus.

CSS, clinical summary score; eGFR, estimated glomerular filtration rate; KCCQ, Kansas City Cardiomyopathy Questionnaire; SD, standard deviation.

Supplemental Figure 1.

Title: Heatmap of Correlation Between Changes in Trial Endpoints and Changes in Metabolites.

Caption: Heatmap cluster correlation matrix is depicted for the relationship between changes in trial endpoints (KCCQ-OSS, KCCQ-CSS, and NT-proBNP) with change in metabolites from baseline to 12 weeks in the entire metabolomics substudy. See Supplementary Table 1 for abbreviations. CSS, clinical summary score; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide. OSS, overall summary score.